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Estimating instantaneous energetic cost during gait adaptation

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Key words: energetics, gait, adaptation, indirect calorimetry, metabolic cost

21 1. INTRODUCTION

22 Steady state measurements of metabolic energetic cost have provided valuable insight into why and
23 how we walk the way we do. Energetic cost, in this context, refers to the input energy required to
24 power the cellular processes underlying the body's movement. This energy is liberated from glucose,
25 fats, and other stored foodstuffs in a reaction that requires oxygen and produces carbon dioxide (3).
26 Consequently, energetic cost is typically measured indirectly by quantifying the oxygen and carbon
27 dioxide in respiratory gases (2, 16). These measurements have demonstrated that we select the most
28 fundamental characteristics of our gait—such as speed, step frequency and step width—so as to
29 minimize energetic cost per distance travelled (4, 5, 8, 9, 17, 23, 29, 35, 36, 40). Cost measurements
30 have also allowed the quantification of energetic penalties imposed by various gait disabilities, and the
31 evaluation of the effectiveness of rehabilitation interventions at mitigating these added costs (5, 35, 36).
32 Equipment and wearable devices, be it backpacks (12, 15), prosthetics (25, 41), orthoses (10, 24), or
33 running shoes (6), have been assessed, iteratively designed, and ultimately improved based on cost
34 measurements.

35 The relationship between the body's instantaneous energy demands (instantaneous energetic cost) and
36 that measured from respiratory gases (measured energetic cost) is complicated. Consider, for example,
37 oxygen consumption measured at the mouth. Muscles meet their instantaneous energy demands for
38 force generation using ATP, a form of stored energy. While ATP is immediately replenished using
39 another form of stored energy, creatine phosphate, the mitochondrial dynamics that use oxygen and
40 foodstuffs to replenish creatine phosphate are rather slow (1, 7, 22, 30). There are still further delays
41 before mitochondrial oxygen consumption is reflected in respiratory gases due to blood circulation
42 from muscle to lungs (13), oxygen exchange between the blood and the lungs, and then lung ventilation
43 itself. The relationship between instantaneous and measured cost cannot be determined by simply
44 adding up these component time delays because blood gases are under tight neural control (28), and

these controllers impose their own dynamics. For example, rapid increases in ventilation are often seen at the onset of exercise (28), preloading the body in anticipation of future mitochondrial oxygen requirements. Consequently, energetic cost as measured at the mouth can occur in advance of any actual energy use by muscle. An additional complicating factor is the discrete nature of breathing—while muscles may be continuously consuming the body’s oxygen, the lungs only replenish oxygen with each breath and each breath may be of drastically different volume. Irregularities in both depth and timing of breaths create noisy breath-by-breath estimates of energetic cost that do not reflect true fluctuations in muscle energy use (14, 20). In summary, the relationship between instantaneous and measured energetic cost is complicated by mitochondrial dynamics, body transit delays, and respiratory control mechanisms, and then further obscured by high breath-by-breath variability.

It is due to these complexities that energetic cost is traditionally only measured during long bouts of constant intensity conditions. By discounting non-steady state regions of cost measurements, the rate at which the oxygen is entering the body is allowed to reach equilibrium with the rate at which cellular processes are consuming it. By averaging over minutes of data, high breath-by-breath ‘noise’ is overcome and the measured energetic cost then accurately matches the instantaneous energetic cost. While these processing techniques have served us well over the past century, they restrict the research questions that can be effectively answered. Long-duration steady-state conditions, such as those experienced on a treadmill, are the exception rather than the norm during real-world walking (21). In truth, we are continually adjusting our gait to meet the demands of a changing environment and the energetic cost under these real-world conditions is essentially unknown.

Here, we expand on traditional methods of assessing energetic cost with the primary purpose of developing a technique to estimate instantaneous energetic cost during gait adaptation. We first characterized the dynamic relationship between instantaneous and measured energetic cost during walking. To accomplish this, we enforced known changes in instantaneous energy use (input)—by

prescribing changes to subjects' walking speed and step frequency—and measured the respiratory responses in measured energetic cost (output; Figure 1A). We then modeled the body as a dynamic system that maps instantaneous to measured energetic cost (Figure 1B). Next, we used this model to test two approaches for estimating instantaneous energy use from respiratory measures. The *inverse model approach* is perhaps the most intuitive—the actual measured energetic cost is smoothed and then passed through the inverse of the identified model to produce an estimate of the instantaneous energetic cost (Figure 1C). The *forward model approach* estimates instantaneous energetic cost as the input that when passed forward through the identified model produces an estimate of measured cost that best fits the actual measured energetic cost response (Figure 1D).

2. METHODS

Ten adult subjects (body mass: 67.1 ± 6.0 kg; height: 173.7 ± 5.2 cm; mean \pm SD) with no known musculoskeletal or cardio-pulmonary impairments participated in this study. Simon Fraser University's Office of Research Ethics approved the protocol, and participants gave their written, informed consent before experimentation. Experiments were performed over two or three days, with no more than two hours of walking per day to reduce fatigue effects.

2.1 Enforcing rapid changes in instantaneous energetic cost

Subjects were instrumented with indirect calorimetry (VMax Encore Metabolic Cart, ViaSys, IL, USA) and all walking was performed on an instrumented treadmill (FIT, Bertec Corporation, MA, USA). To habituate subjects to the experimental set up, they walked at a range of treadmill walking speeds (0.75, 1.00, 1.25, 1.5, and 1.75 m/s) for a minimum of 10-minutes at each speed (31, 33, 34). Subjects next completed a series of enforced rapid changes in gait. The treadmill speed (walking speed) and metronome frequency (step frequency) were rapidly and simultaneously increased or decreased using custom written software (Simulink Real-Time Workshop, Mathworks Inc., MA, USA), in order to

evoke a step-like change in instantaneous energetic cost (Figure 1A). We chose to not only alter speed, but also step frequency because people often take tens of seconds to adjust their step frequency to steady state following perturbations in treadmill walking speed (27, 33). Metronome frequency was set at the subjects' preferred step frequency at each speed, defined as the average step frequency during the final 3-minutes of walking in the habituation trials. Step frequency for an individual step was calculated as the inverse of the time between foot contact events, identified from the characteristic rapid fore-aft translation in ground reaction force center of pressure (32). The treadmill speed alternated between 6-minute periods at a base speed of 1.25m/s and 6-minute periods above or below this base speed (1.5 or 1.75 m/s, and 0.75 and 1.00 m/s, respectively). This resulted in eight different changes in gait (conditions), including step-like changes up-to and down-from the non-base speeds of 0.75, 1.00, 1.5, 1.75 m/s. Speed presentation order was randomized. We designed these changes to have differing direction (increase or decrease in speed) and magnitude (absolute speed change of 0.25 or 0.50 m/s) in order to test if the identified energetic cost dynamics differed across conditions. To compensate for the variable nature of breath-by-breath measurements and to further control for order effects, we had subjects complete a second day of testing in which they repeated the enforced gait changes twice with a newly randomized order, giving us a total of three repeats for each of the eight conditions.

2.2 Modeling the relationship between instantaneous and measured energetic cost

Whipp, Wasserman and colleagues have previously modeled ventilatory gas dynamics during non-steady state cycling (37, 39). Given step changes in work rate, they found the oxygen uptake and carbon dioxide output could be well described by first-order differential equations with an accompanying time delay. Here, we use their model as a starting point for our modeling efforts while recognizing that gas kinetics during walking and cycling are not constrained to have identical dynamics. We modeled the relationship between the instantaneous energetic cost (our input) and the measured cost (our output) as a single dynamic process comprising a time-delayed first-order linear

ordinary differential equation. The mathematical representation of this model expressed in the frequency domain, takes the form:

$$Y(s) = H(s)X(s), \quad (1)$$

where

$$H(s) = \frac{A}{\tau s + 1} e^{-\delta s}, \quad (2)$$

$X(s)$ is the input instantaneous energetic cost, and $Y(s)$ is the output measured energetic cost. The parameter τ is a time constant characterizing the rate of change, A represents the amplitude of the change, and δ is a time delay. One may understand this model as a low-pass filter, where a rapid change in input (instantaneous energetic cost) will result in a slow and smoothed output response (measured energetic cost), and the amount of slowing and smoothing will increase with the magnitude of τ . Thus, if one were to see very quick changes in measured respiratory energetic cost, it would mean there was an exceptionally large and rapid change in the underlying instantaneous energetic cost. One might also understand this model in terms of its response to a step input, where the produced response would take the form of an exponential rise to steady state with a delay between the step input and the beginning of the response.

To fit this model to our data, we analyzed three minutes of metabolic data prior to each gait change and six minutes of data following the gait change. The magnitude of each trial was normalized to unity to allow us to compare and average the steps of differing magnitude and direction. To accomplish this normalization, we first subtracted the steady-state value before the gait change (the average of minutes -3 to 0) and then divided by the amplitude of the change (the average of minutes 3 to 6). Note that this normalization process does not affect any dynamics in the measured cost response. To solve for our unknown model parameters (τ and δ), we used weighted least-squares optimization to minimize the residuals between our model and measured data. The optimization uses the Levenberg-Marquardt

algorithm and was implemented with MATLAB's *nlinfit* function. Due to prior normalization, best-fit amplitudes had a value of one ($A = 1$). In order to avoid known convergence issues with delayed dynamic models (19), we visually confirmed the accuracy of the fitted time delays. We assessed the goodness-of-fit of our estimated parameters by calculating the R^2 value between the model and our measured data. As a test of model sufficiency we also evaluated whether the addition of second process, modeled as an additional time-delayed first-order linear differential equation, produced a better fit to our data.

To test whether the same model holds regardless of magnitude or direction, we first separately fit our model to each of the eight conditions (grouped only across repeats). We then used repeated measures ANOVA to test for differences in our solved parameters between the different magnitudes and directions. If appropriate, we then grouped trials of the same direction (increase or decrease in speed) or magnitude (absolute speed change of 0.25 or 0.50 m/s) and tested for differences using a Student's paired t-test. For all tests, we accepted $p < 0.05$ as statistically significant.

2.3 Estimating instantaneous energetic cost during dynamically changing gait

We next assessed if our solved model could be used to estimate instantaneous energetic cost from measured breath-by-breath energetic cost. To accomplish this, we had two representative subjects return for a third day of testing. Our goal was to enforce instantaneous energetic cost profiles that differed from those upon which our model was based. To design varying instantaneous energetic cost input profiles, we leveraged the fact that subject's energetic cost will increase as their step frequency deviates from preferred (18, 29). To quantify this relationship, our test subjects first walked on the treadmill at 1.25m/s for six minutes at nine enforced step frequencies that were at, above, and below preferred ($0, \pm 5, \pm 10, \pm 15, \pm 20$ % deviation from preferred step frequency). For each enforced step frequency, we took an average of the final three minutes of steady-state energetic cost data, leaving us

with nine data points that we then fit with a cubic polynomial (Figure 2B). Note that during these steady-state regions, the average measured energetic cost is equivalent to the average instantaneous energetic cost, as the gas exchange measured at the mouth has reached equilibrium with the gas exchange occurring at the muscle tissue level.

Next, the solved polynomial was used to design step frequency profiles that, at constant treadmill speed of 1.25m/s, would evoke three distinct input muscle energy use profiles—a step, a ramp, and an adaptation profile (Figure 2A). The step profile, although the same shape as the original input profile on which we based our model, imposed different physical constraints on the subject, as treadmill speed was held constant and only step frequency was rapidly increased. The ramp profile was markedly different from that of the step in that step frequency was gradually increased over the course of minutes. The adaptation profile was designed to mimic a fast adaptation, where a subject's instantaneous energetic cost may initially step up in response to a perturbation and then rapidly decay within tens of seconds. For each trial, treadmill speed was held constant at 1.25m/s and the subject was asked to match their steps to the changing metronome frequency (Figure 2C) while we measured energetic cost. The subjects completed three repeats for each input profile shape in randomized order.

We then used two different approaches to estimate instantaneous energetic cost from measured cost, each approach having distinct strengths and drawbacks. Recall that for each subject, we have solved for an individualized model that maps instantaneous to measured energetic cost. Therefore, the inverse of this model will do the opposite: map measured to instantaneous energetic cost. This is the basis of our inverse model approach (Figure 1C). By passing a subject's measured energetic cost data through their inverse model, we can directly compute the instantaneous energetic cost. However, it was necessary to first smooth the measured data. Passing unsmoothed data through the inverse model, which functions like a high pass filter, would effectively amplify high frequency components in the measured signal and these high frequency components tend to be dominated by the breath-by-breath noise. Although a low

pass filter could be used to first attenuate noise, it would indiscriminately attenuate all high frequency inputs, which may include rapid changes in instantaneous energetic cost that we are seeking to identify. Instead, to estimate the shape of the underlying energetic cost profiles, less the noise, we fit each trial of measured data with polynomials. A constrained least squares optimization, implemented using MATLAB's *lsqlin* function, was used to solve for the best-fit polynomial parameters. Polynomial order was set such that no systematic pattern was observed in the residuals. The fitted curve was required to pass through the initial steady state value (0 after normalization) at the point of perturbation and had to reach steady state (1 after normalization) in the last 3 minutes of the trial. These constraints are reasonable given that the prescribed step frequencies were at steady state during these regions. We did not constrain the initial slope of the polynomial allowing for rapid initial changes in the smoothed cost. Our forward model approach can be used in situations where the experimenter has a good first approximation of the shape of the instantaneous energetic cost profile (Figure 1D). This shape is described with a set of parameters that are then optimized so that the generated input profile, when run through the subject's model, produces an estimate of measured cost that best fits the actual measured energetic cost response. We used a Nelder-Mead Simplex method, implemented with MATLAB's *fminsearch* function, to solve for the optimal parameter values. For the step input, a single parameter was optimized: the time of onset of the step. For the ramp input, two parameters were optimized: the time of onset and the time of offset of the ramp, which together dictate the slope of the ramp. For the adaptation input, three parameters were optimized: the time of onset, the amplitude of the peak, and a decay constant. Note that the initial and final steady-state amplitudes were not optimized, as normalization fixes them at 0 and 1, respectively.

3.0 RESULTS

We found that the dynamic relationship between instantaneous energetic cost and measured energetic

cost could be modeled using a first-order linear ordinary differential equation (Eq. 2). Moreover, we found that the same model appears to hold regardless of the magnitude or direction of the change in gait. We did not identify differing model parameters when each of the eight gait changes, of varying magnitude and direction, were fit separately ($p = 0.102$). When we then grouped across all trials of the same direction (increase or decrease in speed) we again found that parameters did not differ between directions ($p = 0.500$). The same was found when we grouped trials of the same magnitude (absolute speed change of 0.25 or 0.50 m/s) ($p = 0.094$). This indicates that the underlying dynamics were not significantly different irrespective of the applied magnitude or direction of the change in gait. For subsequent analyses all trials for an individual subject have been fit together.

Our model described the dynamics of respiratory metabolic cost reasonably well for most subjects. When compared to the average response, the model accounted for 82-99% of the measured variability (Figure 3). When the model was compared to individual trials, without averaging, 18-87% of the measured variability was explained. This considerably larger range in goodness-of-fit is due to the variability between breaths in measured metabolic cost, and was expected given that we did not attempt to model breath-by-breath dynamics. Adding a second dynamic process, modeled as an additional time-delayed first-order linear differential equation, did not appreciably improve our fits; visually no improvement was evident and on average only an additional $0.9\% \pm 1.0\%$ of the variability was explained (mean \pm SD).

Across all subjects, model fits yielded an average time constant (τ) of 41.9 ± 12.0 s (mean \pm SD). This means that 95% of the response to a step-like change input is completed within three time constants, or 125.6 ± 36.1 s (mean \pm SD). We did not identify time delays (δ) that were discernable from zero for any of the ten subjects. Due to normalization, all amplitudes (A) displayed in Figure 4 have a value of 1. Therefore, the mathematical representation of our model (Eq. 3) simplifies to a transfer function of the form:

$$H(s) = 1/(42s + 1) \quad (3)$$

This model enabled accurate estimates of instantaneous energetic cost from respiratory energetic cost measures. Using both our inverse and forward model approaches, we were able to produce estimates of instantaneous energetic cost from measured energetic cost that well matched the enforced step, ramp, and adaptation profiles (Table 1 and Figure 4). For the step and ramp input profiles, both approaches performed exceptionally well. The R^2 values between the enforced instantaneous energetic cost profile and the model-produced estimates of instantaneous energetic cost were between 0.87-0.99 for individual trials. As a result, averaging measured energetic cost data across the three repeats prior to applying either approach did little to improve our estimates of instantaneous energetic cost. Thus, for the step and ramp profiles, it appears possible to accurately estimate instantaneous cost from a single trial of measured energetic cost data. Single trial estimates of instantaneous energetic cost were less accurate for the adaptation profile. For subject I, individual trial R^2 values were as low as 0.26 and 0.38 for the inverse model approach and forward model approach, respectively. For this subject, averaging measured energetic cost data across the three repeats prior to applying the inverse model approach or forward model approach improved R^2 values to 0.66 and 0.75, respectively. Individual trial R^2 values for the adaptation trials were substantially better for Subject II (0.77-0.88).

4.0 DISCUSSION

We found that a simple first order linear differential equation can approximate transient energetic cost responses during gait. When rapid step-like changes in instantaneous energetic cost were enforced, we observed a single underlying response featuring no discernable delay. On average, subjects took two minutes to reach 95% of the steady state metabolic cost value, with all but one subject reaching 95% steady state within three minutes. These same underlying dynamics held regardless of the magnitude or direction of the change in gait. Despite the collective effect of many sources of complexity—including

256 mitochondrial dynamics, gas stores, transit delays, and cardio-pulmonary control—a simple model
257 explains the transient energetic cost response during walking.

258 This model allowed us to produce reasonably accurate estimates of instantaneous energetic cost from
259 respiratory cost measures. Our two approaches—the inverse model approach and forward model
260 approach—resulted in similar estimates of instantaneous energetic cost, and when compared to our
261 enforced cost profile, R^2 values were typically greater than 0.90. Both methodologies were able to
262 capture rapid changes in instantaneous energetic cost that were prescribed during the step trials, as well
263 as gradual changes and discontinuities that were prescribed during the ramp trials. The poorest
264 estimates of instantaneous energetic cost were found for the adaptation trials, where fitting the rapid
265 decay proved somewhat problematic. These sorts of transient changes in cost are more readily distorted
266 by breath-by-breath noise because there are fewer data points available with which to fit model
267 parameters. Our adaption trial decayed to steady state with a time constant of 60 seconds, which
268 equates to only about 20 breaths. Better estimates may be possible with improved noise removal
269 techniques, improved fitting techniques, or through averaging over a greater number of trial repeats.

270 Overall, the two approaches produced similar and seemingly accurate estimates of instantaneous
271 energetic cost. However, each approach is subject to distinct limitations and requires different
272 assumptions on the part of the user.

273 The inverse model approach requires little advance knowledge of the underlying instantaneous
274 energetic cost profile, but is greatly complicated by breath-by-breath noise. High frequency
275 components of breath-by-breath variability in measured energetic cost are effectively amplified when
276 passed through the model inverse, obscuring estimated instantaneous energetic cost. To reduce their
277 contribution, while retaining our ability to fit fast changing inputs, we first fit the noisy metabolic cost
278 data using a polynomial. We constrained the polynomial to pass through an initial steady state value at
279 the point of perturbation, and to reach steady state at the end of the trial. For an experimenter, these

constraints require that the protocol be designed such that the subject begins and ends in steady state. (These particular constraints are not universal for every experimental paradigm—researchers should identify whatever constraints on the measured data are imposed by the experimental paradigm and use them to their fitting advantage.) Although we made no assumptions about the shape of the profile between the beginning and end steady state regions, complex profiles would not be fit well by a low order polynomial. In such situations higher order polynomials, splined polynomials, or all together different functions may be necessary to accurately fit the measured energetic cost profiles. This will inevitably introduce subjectivity, as the experimenter will be required to make decisions about what profile changes are ‘true’ and what is simply ‘noise’.

Estimating instantaneous energetic cost using the forward model approach requires some advance knowledge of the profile shape. This knowledge may be based on the study design or additional measurements. For example, if the study design calls for a novel force to be rapidly applied to a limb one may reasonably assume an abrupt increase in instantaneous energy use, followed by an exponential decay as the subject adapts to the new force. One need not know the timings and magnitudes of the initial increase and subsequent decay as the forward approach employs optimization to estimate their values. Alternatively, one may deduce the profile shape from a measured physiological variable, such as the time course of adjustments to step frequency or muscle activity. It is also possible that the experimenter has a range of hypotheses about what the input profile shape may be. These hypotheses can be evaluated by optimizing each candidate input profile and testing which one provides the best fit. To illustrate this, we fit optimal step, ramp, and adaptation profiles to each of the three responses and found that each response was best fit by its respective profile shape (e.g. the enforced ramp was best fit by a ramp profile). Because the experimenter must make assumptions about the underlying profile shape, the forward approach introduces a bias based on the experimenter’s expectations. Moreover,

303 there may be situations where the experimenter does not have a reasonable first approximation of the
304 input profile shape.

305 In addition to the approach specific limitations described above, there are four more general limitations
306 to our methodology and analysis. First, we treat our enforced instantaneous energetic cost profiles as a
307 gold standard to which we compare our model estimates. Although we attempted to enforce a specific
308 cost profile by controlling walking speed and step frequency, other uncontrolled gait parameters, for
309 example stance time or muscle activity, may have caused instantaneous energetic cost to deviate from
310 our desired input profile. As a consequence, our estimates may be better or worse than presented.

311 Second, the identified model and its average parameters only apply to adult humans. Differences in size
312 and phylogenetic history are both likely to alter the dynamic relationship of other animals from that in
313 adult humans. Similarly, the identified model and its average parameters only apply to walking. While
314 we found that a single process accurately captures the identified dynamic relationship between
315 instantaneous and measured energetic cost, Whipp and colleagues have repeatedly found that there are
316 two important processes in cycling, perhaps reflecting a difference in cardio-pulmonary control
317 between the two tasks (37, 38). A fourth limitation of our model is that it can only be applied to
318 walking tasks within the tested metabolic cost range. At metabolic rates above 400W, many subjects
319 may breach the anaerobic threshold, causing oxygen stores to be depleted faster than they can be
320 replenished and rendering our measured energetic cost a poor estimate of the underlying instantaneous
321 energetic cost. At metabolic rates below 100W it is possible that more complex dynamics exist at the
322 onset of exercise, as first described by Whipp and colleagues (37). Overall, our exact model can be
323 used to estimate instantaneous energetic cost of walking at metabolic rates ranging from 100W to
324 400W. Outside of this range, care should be taken to first identify the underlying dynamic relationship
325 between instantaneous and measured energetic cost before applying our inverse or forward model
326 approach.

327 Our methodology may prove useful for both post-hoc and real-time estimation of energetic cost. Its
328 accuracy benefits from a personalized model for each subject, but for some situations, it may suffice to
329 use the average dynamic model identified in the current experiments. As an initial test of this
330 possibility, we simulated measured energetic cost to an adaptation input profile for a subject with an
331 exceptionally slow time constant of 60s. We then compared instantaneous cost estimates using this
332 subject specific time constant to that obtained if we assumed our average time constant (42s). Using the
333 average time constant still made it clear that instantaneous cost adapted by demonstrating the
334 characteristic rapid increase followed by a slower decay. As to be expected, R^2 values dropped when
335 using the average time constant, but nearly 90% of the variability was still explained. This general
336 model is particularly useful because it allows experimenters to return to previously measured energetic
337 cost data and estimate instantaneous energetic cost without the need for a subject specific model of cost
338 dynamics. Another use for the identified dynamic model is real-time estimation of instantaneous cost.
339 Kalman filters, and similar algorithms, leverage dynamic models of the system to help correct for noise
340 and delays (11, 26). Real-time estimates of instantaneous energetics may prove useful for biofeedback,
341 manipulating gait training based on energetic cost, or simply for online determination of when a
342 research subject has reached steady state.

343 An ability to assess instantaneous energetic cost during non-steady gait could unveil new insights into
344 walking. People rarely experience metabolic steady-state conditions; less than 1% of real-world
345 walking bouts last the requisite five minutes (21). The fields of locomotor adaptation and learning aim
346 to shift our scientific focus from the steady state to this real-world behaviour. Energetic concepts—
347 such as economy, efficiency, and least effort—are often used to explain adaptations to novel
348 environments or tasks. Yet, as researchers work to understand the neuronal circuitry involved in gait
349 adaptation, and quantify the timescales over which adaptation occurs, they have been unable to
350 effectively make direct comparisons to energetic cost during the adaptation itself. An understanding of

351 the role of energy use may help us understand how we adapt to changing environments, how we
352 compensate for injury or motor control deficits, and how we learn new tasks. By presenting a
353 methodology for assessing instantaneous energetic cost during adaptation and other non-steady gait
354 conditions, we aim to provide our field with a tool with which we can investigate previously
355 unanswerable questions.

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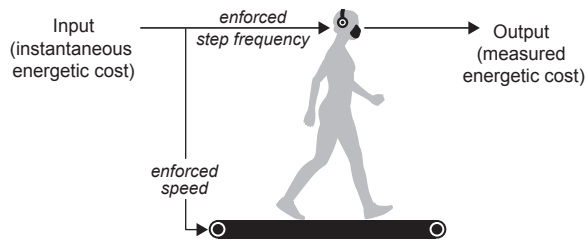
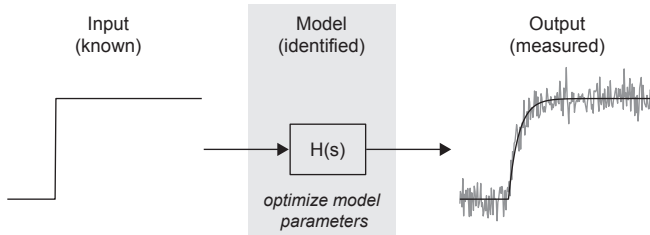
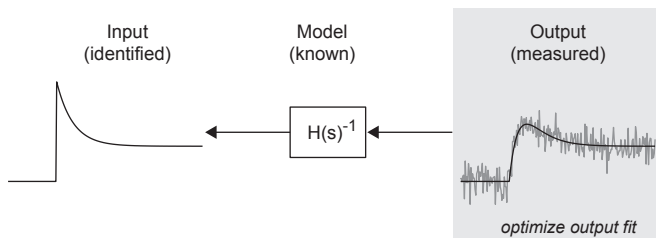
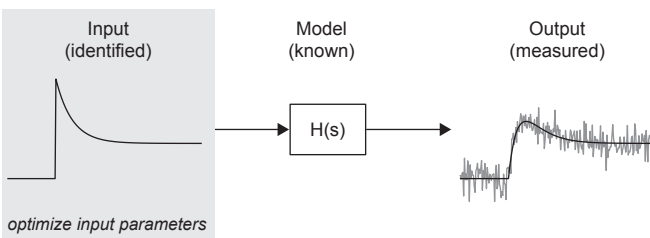
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FIGURES**A. Experimental Set-Up****B. Estimating a Dynamic Model for Energetic Cost****C. Estimating Instantaneous Energetic Cost using the Inverse Model Approach****D. Estimating Instantaneous Energetic Cost using the Forward Model Approach**

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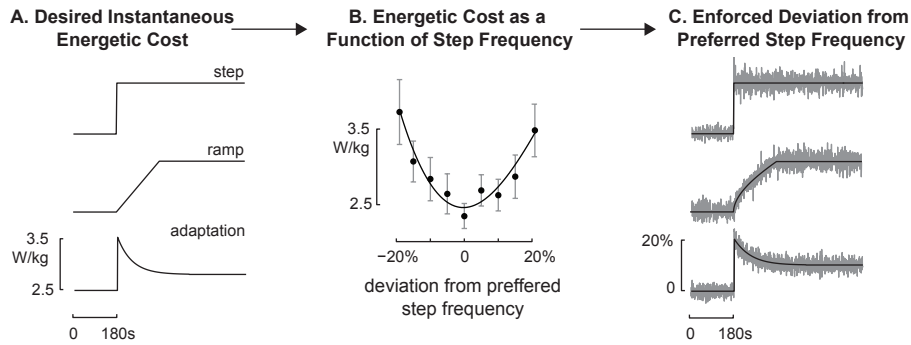
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Figure 1: Experimental design. A. Experimental Set-up. To evoke known changes in instantaneous energetic cost, subjects' walking speed (treadmill speed) and step frequency (metronome frequency) was enforced and the resulting breath-by-breath energetic cost response was measured using indirect calorimetry. B. We then modeled the relationship between instantaneous energetic cost (input) and measured energetic cost (output). Using this model we estimated instantaneous energetic cost from the

460 measured energetic cost response using two approaches. C. When using the inverse model approach,
461 noisy output data was fit with a constrained polynomial, which was then passed through the inverse of
462 our identified model to produce an estimate of instantaneous energetic cost. D. When using the forward
463 model approach, we assumed the general shape of the input profile is known and described it by a set
464 of parameters, which were then optimized so that the input profile, when run forward through our
465 identified model, generated an output profile that best fit our measured output. Grey shaded boxes have
466 been used to highlight what parameters were optimized for each processing technique.

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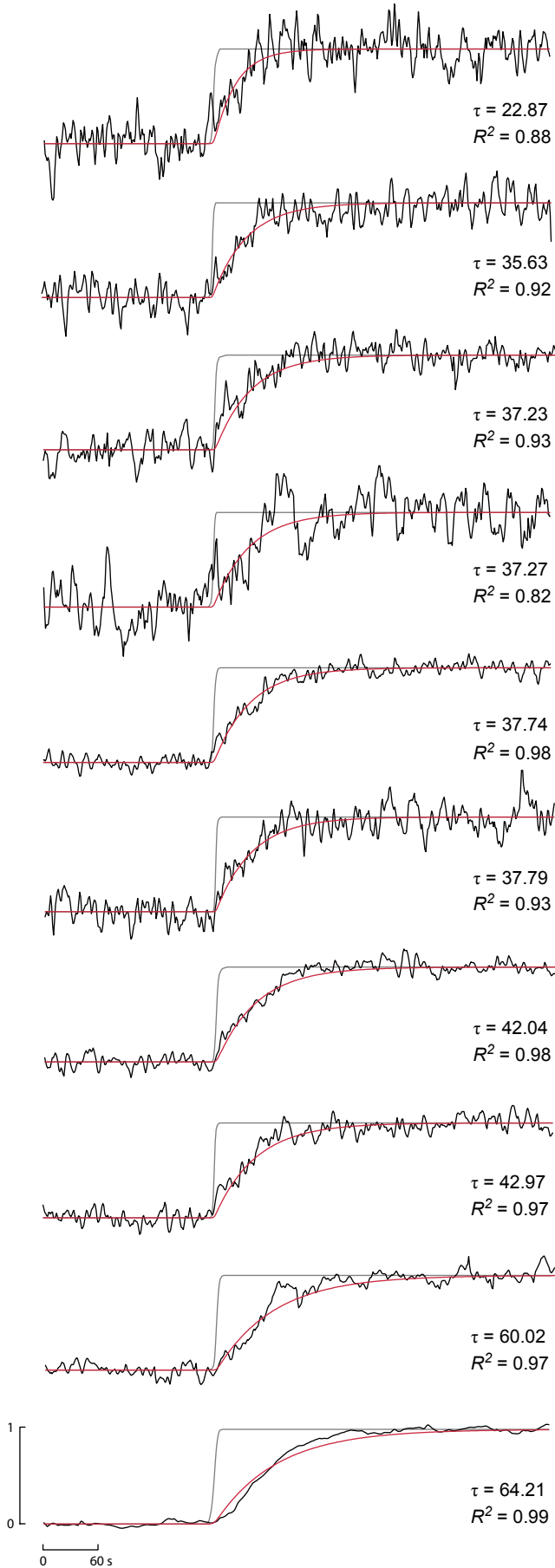
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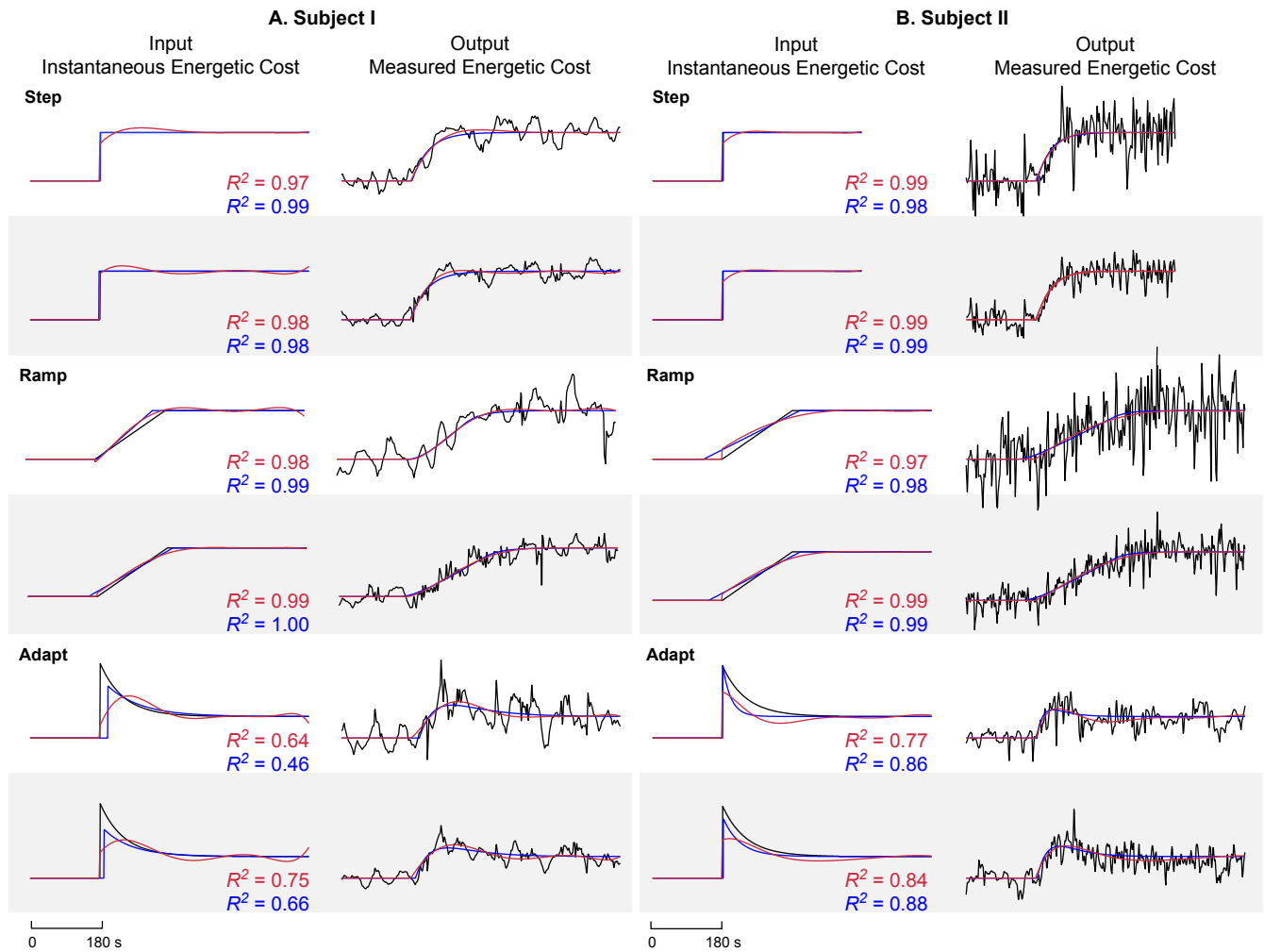
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Figure 2: A. We sought to enforce three differing but known input changes in instantaneous energetic cost. B. In order to identify what step frequency profiles would evoke these desired changes in instantaneous energetic cost, we identified each subject's relationship between energetic cost and deviation from preferred step frequency. C. Using the solved relationship between energetic cost and step frequency, we designed step frequency profiles that would evoke our desired change in instantaneous energetic cost. The black line illustrates the step frequency commanded with a metronome and the grey line illustrates the subjects actual step frequency. All presented data is from Subject I.



478 Figure 3. Modeling the measured energetic cost response. The average measured energetic cost
479 response (black line) to 24 rapid changes in instantaneous energetic cost (grey line) is shown for each
480 subject. The red line illustrates the model that best fits each subject's response. Model time constants
481 (τ) and R^2 values for each fit are presented on the right hand side of each panel. Before we averaged the
482 data, we normalized all instantaneous and measured energetic cost changes to unity by subtracting the
483 initial steady-state values and dividing by the amplitude of the final steady-state values.

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486 Figure 4: Estimating changes in instantaneous energetic cost. A. Subject I results. The enforced
 487 instantaneous energetic cost (input) and measured energetic cost response (output) are shown in black,
 488 in the left and right panels respectively for the step, ramp, and adaptation profiles. The red lines
 489 represent estimates from the inverse model approach, and the blue lines represent estimates from the
 490 forward model approach. R^2 values calculated between the enforced instantaneous energetic cost
 491 profiles and the inverse model approach estimates of muscle energy use are shown in red text, while
 492 that for the forward model approach estimates are shown in blue text. Data corresponding to the
 493 median trial and average trial (shaded box) have been plotted. B. Subject II results. Note that for the

494 Subject II, the step trials lasted only 540s as apposed to 720s due to a protocol change during data
495 collection. Despite this change, the time given was sufficient to allow the subject to reach steady state,
496 allowing us to process these trials in the same manner as all other trials.

497

498 Table 1: R^2 values between the enforced and the model-produced estimates of instantaneous energetic
 499 cost for both the inverse model and forward model approach. We collected three repeats for each of the
 500 step, ramp, and adaptation input profiles. R^2 values from the three repeats have been ordered from
 501 highest to lowest. To produce the average value, we averaged the measured energetic cost data across
 502 the three repeats prior to applying the inverse model or forward model approach. Note that for each
 503 subject and each approach, we have plotted the data corresponding to the median and averaged trials in
 504 Figure 5.

Input	Trial	Subject A		Subject B	
		Inverse	Forward	Inverse	Forward
Step	best	0.98	0.99	0.99	0.99
	median	0.97	0.99	0.99	0.98
	worst	0.94	0.93	0.94	0.87
	average	0.98	0.98	0.99	0.99
Ramp	best	0.99	0.99	0.99	1.00
	median	0.98	0.99	0.97	0.98
	worst	0.98	0.99	0.89	0.93
	average	0.99	1.00	0.99	0.99
Adapt	best	0.90	0.96	0.84	0.82
	median	0.64	0.46	0.77	0.86
	worst	0.38	0.26	0.79	0.78
	average	0.75	0.66	0.84	0.88

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